

REMARKS

Claims 5, 9-16, 19-23, 26 and 30-64 are pending and under examination in the subject application. Claims 5, 26, 32, 33, 39, 54, 57 and 58 have been amended above. Support for the amendments can be found throughout the application. In particular, support for the amendment to claims 5, 26, 32, 33, 39, 54, 57 and 58 can be found at, for example, page 7, lines 8-13. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicants have reviewed the rejections set forth in the Office Action mailed April 20, 2005, and respectfully traverse all grounds for the reasons that follow.

Applicants would like to thank Examiner Lu for extending a personal interview with Applicants and Applicants' representative on August 9, 2005. The amendments above and remarks below are believed by Applicants to substantially conform to the subject matter discussed in the interview and result in the Examiner's reconsideration of the rejections.

Rejections Under 35 U.S.C. § 102

Claims 5, 13, 32, 39, 45 and 57 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Barany et al., U.S. Patent No. 6,027,889. The Office maintains that Barany et al. describe the detection of nucleic acid sequence differences using coupled ligase detection and polymerase chain reaction (PCR) and further alleges that Barany et al. describe probes having distinct first through fifth portions as recited by the claims. An annotated version of Figure 12 is asserted to show the five distinct portions. The Examiner also alleges that the claims do not require that a capture probe specifically hybridize to an adapter sequence.

The claims are directed to a method of determining the identification of a nucleotide at a detection position in a target sequence. The claimed method includes hybridizing first and second ligation probes to first and second target domains of a target sequence. Either the first or second ligation probe contains a fifth portion that includes an adapter sequence distinct from other portions of the ligation probes. Although not conceding that the Barany et al. describes probes having five distinct portions as claimed by Applicants, the claims also recite that a capture probe of the array is distinct from the target sequence and specifically hybridizes to the adapter sequences as suggested by the Examiner. Therefore, the claims specify five distinct

portions within the probes and specific hybridization of the capture probe to the adapter sequence. Accordingly, the claims cannot be anticipated by Barany et al. at least because Barany et al. describes non-specific hybridization of the alleged capture probe to different adapter sequences (mutant and normal). In light of the amendment, Applicants submit that this ground of rejection is moot and respectfully request its withdrawal.

Rejections Under 35 U.S.C. § 103

Claims 14-16, 34, 46-48 and 60 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al. in view of Walt et al., U.S. Patent No. 6327,410. The Office concedes that Barany et al. does not disclose the array as claimed but maintains that one skilled in the art would have been motivated to use the array described by Walt et al. because the replacement of one array type with another type would not change the steps of the experiment. The Office maintains that its burden has been met, alleging that all elements of the claimed ligation probes have been described, but notes that the claims do not require that a capture probe specifically hybridize to an adapter sequence.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (C.C.P.A. 1974); M.P.E.P. §2143.03. Although not conceding that Barany et al. describes probes having five distinct portions as claimed, Applicants respectfully maintain that the Office has not established a *prima facie* case of obviousness, at least because all the elements of the claimed ligation probes are neither taught or suggested by the cited art. The base claims from which the rejected claims depend now recite that the capture probe of the array is distinct from the target sequence and specifically hybridizes to the adaptor adapter sequence of a ligation probe. As described above, Applicants have claimed specific hybridization between the capture probe and an adapter sequence, which is an element not described by the cited combination. Rather, Barany et al. describes non-specific hybridization of the alleged capture probe to both mutant and normal sequences. In the absence of a teaching or suggestion in the cited references of each element of the claimed ligation probes, the Office has not established a *prima facie* case of obviousness of the rejected claims under 35 U.S.C. § 103(a).

Further, the cited references neither provide a suggestion or motivation to identify a nucleotide at a detection position in a target sequence using a fifth portion consisting of an adapter sequence that specifically hybridizes to a capture probe and is distinct from a target sequence because the method of Barany et al. is directed to ligase detection reaction (LDR), which relies on differences in hybridization between the probe and target sequences for detection of the mutant sequence compared to the normal sequence. Absent a suggestion or motivation to use a capture probe that specifically hybridizes to the adapter sequence, the claims cannot be obvious over the cited art. Because the cited combination of references neither describe or suggest all elements of the claimed invention nor provide a motivation to detect amplicons using specific hybridization between capture probes and adapter sequences, Applicants respectfully request that this ground of rejection be withdrawn.

Independent claims 26, 33, 54, 58 and dependent claims 10, 13, 19-22, 31, 35, 42, 49-52, 56, 59 and 61 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Zhang et al, U.S. Patent No. 5,876,924, in view of Barany et al. The Office asserts that Zhang et al. describes two oligonucleotide probes, a capture/amplification probe and an amplification probe, that contain five distinct portions and hybridize adjacently on a target nucleic acid. The Office concedes that Barany et al. does not describe a step (a) of claims 26, 33, 54 and 58, directed to providing a support on which the target sequence is immobilized, but alleges that the streptavidin beads described by Zhang et al. provide this element since the claimed steps are not required to be performed in order. The Office further alleges that one skilled in the art would have been motivated to replace the ligation method of Zhang et al. with that described by Barany et al. because it would not change the result and that there is no change in the basic principle or design between the two methods described in the cited references.

As with the previous rejections relying on Barany et al., the claimed invention cannot be obvious over the cited combination of Barany et al. in view of Zhang et al. because Barany et al. fails to teach or suggest specific hybridization of the claimed capture probe to an adapter sequence that is distinct from the target sequence. The combination of Zhang et al. for allegedly describing a solid support or for providing motivation for the substitution of allegedly similar amplification methods does nothing to cure this deficiency. Moreover, the capture/amplification probe described by Zhang et al. also fails to describe specific hybridization with an adapter

sequence because it uses ligand binding probes. Accordingly, absent a teaching, suggestion or motivation to use a capture probe that specifically hybridizes to an adapter sequence, the claims cannot be obvious over the cited art. Because the cited combination of references neither describe or suggest all elements of the claimed invention nor provide a motivation to detect amplicons using specific hybridization between capture probes and adapter sequences, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 11, 12, 43 and 44 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al. in view of Zhang et al. as applied above and further in view of Gebeyehu et al., U.S. Patent No. 4,921,805. Gebeyehu et al. is cited for allegedly describing an intercalator attached to a bead to separate non-hybridized probes from hybridized probes as claimed. Similarly, claims 9, 23, 30, 41, 53, and 55 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al. in view of Zhang et al., as applied above, and further in view of Seradyn Particle Technology. Claims 37 and 63 also stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al. in view of Zhang et al., and further in view of Monforte et al., U.S. Patent No. 5,830,655. Claims 36 and 62 stand rejected under 35 U.S.C. § 103(a) over the above combination of references and further in view of Brown et al., U.S. Patent No. 5,807,522, whereas claims 38 and 64 stand rejected under 35 U.S.C. § 103(a) over the combination of Barany et al. in view of Zhang et al. and Monforte et al. and further in view of Johnson et al.

All of the above claims depend from one or more of the independent claims 5, 26, 32, 33, 39, 54, 57 and 58. Accordingly, the dependent claims contain all the limitations of the base claims from which they depend. As set fourth above, neither Barany et al. in view of Walt nor Barany et al. in view of Zhang et al. provide all elements of the claimed invention or a motivation to combine the respective references. Accordingly, the independent claims are unobvious over the cited combination of references. The above tertiary references are cited allegedly for describing a further element found within the dependent claims. Because the cited art fails to teach, suggest or provide a motivation for each and every element of the claimed invention and because the tertiary references are directed to further elements within the dependent claims, the citations to Gebeyehu et al., Seradyn Particle Technology, Monforte et al. or Johnson et al. cannot cure the deficiencies of the primary and secondary references.

Accordingly, the cited art cannot teach or suggest all elements of the claimed invention and withdrawal of this ground of rejection is respectfully requested.

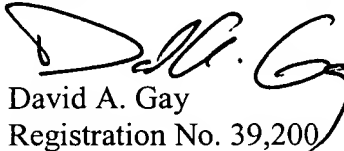
CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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